acid molecule; wherein said compound modulates methionine synthase reductase biological activity in said subject in an amount sufficient to treat said cancer, cardiovascular disease, or a neural tube defect.

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34. (New) The method of claim 33, wherein said subject has cardiovascular disease.

REMARKS

The invention features a method for detecting, preventing, and treating an increased or decreased likelihood of hyperhomocysteinemia, neural tube defects, cardiovascular disease, or cancer as well as a method for detecting and preventing Down's syndrome. The invention further features administering therapeutic compounds for treating, preventing, or reducing the risk of neural tube defects, cardiovascular disease, or cancer, and for preventing or reducing the risk of Down's syndrome.

Examination of pending claims 1-11, 13, 14, and 21 is reported in the Office Action mailed March 5, 2000. Claims 1, 3, 4, and 5 were rejected under 35 U.S.C. § 112, second paragraph and claims 1-11, 13, 14, and 21 were rejected under 35 U.S.C. § 112, first paragraph. Claims 2 and 5 were rejected under 35 U.S.C. § 102(b). Each of these remaining rejections is addressed below.

Support for the Amendments

The amendments to claims 1-3, and 5 are provided herewith to more clearly recite the invention the Applicants intend to claim. Support for amended claim 1 is found in the specification on page 33, lines 13-16. Support for new claims 22, 24, and 25 is provided on page 26, lines 11-24; page 27, lines 1-8; and page 36, lines 2-11, of the specification. Support for new claim 23 is provided on page 36, lines 12-24, and page 37, lines 1-6, of

the specification. Support for new claim 26 is found in the specification on page 10, lines 17-20. Support for new claims 27, 28, and 31 is provided on page 10, lines 21-25, and page 11, lines 1-8, of the specification. Support for new claim 29 is found in the specification on page 8, lines 14-20, and page 9, lines 13-22. Support for new claim 30 is found in the specification on page 8, lines 21-25, and page 9, lines 1-12. New claim 32 is supported by page 28, lines 19-23, of the specification. Support for new claims 33 and 34 can be found in the specification on page 10, lines 9-20. Further support for all new claims can also be found in claims 1-3, 5-7, 10, and 11 as filed. The title is also amended to reflect the presently claimed invention. No new matter is added by these amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3, and 5 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting a step that recites how methionine synthase reductase biological activity is inhibited in an amount sufficient to treat or reduce the risk of cancer, cardiovascular disease, Down's syndrome, or neural tube defects in a subject.

Applicants have amended claim 1 (from which claims 3 and 5 depend) to specify a method of preventing cancer, cardiovascular disease, Down's syndrome, or a neural tube defect in a subject, by administering a compound selected from the group consisting of a protein, a small molecule, and an antisense nucleic acid molecule, which modulates methionine synthase reductase biological activity in a subject in an amount sufficient to prevent cancer, cardiovascular disease, Down's syndrome, or neural tube defect in a subject. Applicants have also added new claim 33 to specify a method of treating cancer, cardiovascular disease, or a neural tube defect in a subject, by administering a compound from the group consisting of a protein, a small molecule, and an antisense nucleic acid molecule, which modulates methionine synthase reductase biological activity in a subject in an amount sufficient to treat cancer, cardiovascular disease, or a neural tube defect in a

subject. Accordingly, this rejection may now be withdrawn.

Claims 4 and 5 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the term "claim D." Applicants have cancelled claim 4 (from which claim 5 depended). Accordingly, this rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-11, 13, 14 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner acknowledges that the specification is enabling for demonstrating the correlation between an increased risk of neural tube defects and a combination of the homozygous A66G methionine synthase reductase (MTRR) genotype and a low cobalamin level. The Examiner also acknowledges that the specification demonstrates a correlation between the A66G MTRR mutation and an increased risk for Down's syndrome and coronary artery disease (CAD). Furthermore, the Examiner states that the specification is enabling for the association of homocysteine, folic acid, vitamin B6, and vitamin B12 with cancer and vascular disease.

Rejection for failure to enable the use of agents that modulate MTRR biological activity

However, the Examiner asserts that the specification fails to provide adequate guidance and evidence for the correlation between modulating MTRR biological activity and treating or preventing cancer, cardiovascular disease, neural tube defects, or Down's syndrome in a subject. The Examiner further states that the specification fails to teach where and how to administer an agent that modulates MTRR activity to a subject. Applicants respectfully disagree.

Applicants respectfully assert that pending claims 1-3, 5-11, 13, 14, and 21 and new claims 22-34 are fully enabled by the specification. Numerous examples of therapeutic agents that modulate MTRR biological activity are described in the

specification (see, for example, page 25, lines 3-12). For example, as stated on page 10, lines 9-16, of the specification:

> [T]he invention features a method of treating or preventing cancer, cardiovascular disease, or neural tube defects. The method comprises inhibiting methionine synthase reductase biological activity...[T]he method comprises administering a therapeutically effective dose of a methionine synthase reductase inhibitor to a mammal. The inhibitor may be a methionine synthase reductase anti-sense nucleic acid, a peptide comprising a portion of a mammalian methionine synthase reductase polypeptide, or a small molecule.

In addition, the specification further teaches that individuals with decreased methionine synthase activity have an increased risk for cardiovascular disease, neural tube defects, and cancer (page 2, lines 15-18, and page 33, lines 1-4, of the specification). Since methionine synthase reductase is responsible for maintaining methionine synthase in its activated (reduced) state, compounds that increase MTRR biological activity are useful in the treatment and prevention of cardiovascular disease, neural tube defects, and cancer. As stated on page 35, lines 18-22 of the specification:

> Potentially useful therapeutic compounds that modulate (e.g. increase or decrease) methionine synthase reductase activity or expression may be isolated by various screens that are well-known to those skilled in the art. Such compounds may modulate methionine synthase reductase expression at the pre- or post-transcriptional level, or at the pre- or post-translational level.

Additional therapeutic compounds that modulate (*e.g.*, increase or decrease) methionine synthase reductase activity or expression may be isolated by various screens that are well known to those skilled in the art. In particular, the specification discloses

numerous test compounds that may be assayed for the ability to modulate MTRR biological activity *in vitro*, in cell based assays, in animal models, or in humans (pages 33-35). For example, compounds may be tested to determine their effect on MTRR enzymatic activity, protein levels, promoter activity, and/or mRNA levels (see, for example, pages 26, 27, and 36-40).

Furthermore, as stated in the specification, one skilled in the art of molecular biology can engineer a transgenic mouse by introduction of a transgene with the human MTRR coding sequence into a mouse (see page 22, lines 9-22, and page 39, lines 11-24). This transgenic mouse model can be used as a late-stage *in vivo* screen to test or confirm the ability of various compounds to modulate MTRR biological activity.

Moreover, the specification teaches a variety of formulations that may be used to administer compounds that modulate MTRR biological activity to patients or experimental animals (page 14, line 6, through page 15, line 9; and page 20, lines 1-6). In addition, the specification discloses numerous routes of administration that can be used to provide a sufficient amount of an agent to treat or prevent cancer, cardiovascular disease, Down's syndrome, or a neural tube defect (see page 41, lines 7-19). One skilled in the art would appreciate that standard clinical trials can be used to optimize the dose or dosing frequency for a particular agent. As numerous examples of agents that modulate MTRR biological activity and numerous assays that may be used to identify additional agents are described and enabled in the specification, this aspect of the rejection should be withdrawn.

Rejection for failure to enable gene therapy

In response to the Examiner's argument that gene therapy is unpredictable, Applicants note that amended claim 1 and new claim 33 recite the administration of a compound selected from the group consisting of a protein, a small molecule, and an

antisense nucleic acid molecule. Amended claim 2 and new claims 26 and 27 recite the administration of a metabolite or cofactor. Applicants further note that the specification enables the administration of a variety of proteins, small molecules, antisense nucleic acids, cofactors, and metabolites.

As set forth in MPEP § 2164.08,

> "All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims. See, *e.g.*, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
>
> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971)."

Thus, the present claims are sufficiently enabled by the numerous embodiments disclosed in the specification. Accordingly, this aspect of the rejection may be withdrawn.

Rejection for failure to enable the use of a cofactor or metabolite

The Examiner also asserts that the invention is not enabling for a method of treating or preventing cancer, cardiovascular disease, neural tube defects, or Down's syndrome by administering a metabolite or cofactor. Applicants respectfully disagree.

The specification teaches that "[a]lterations in [the] metabolism of folates, homocysteine, methionine, vitamin B12, and S-adenosylmethionine are associated with...hyperhomocysteinemia [which] may be associated with a higher than normal risk for cardiovascular disease" and Down's syndrome (page 62, lines 3-7, and page 63 of the specification). The specification further teaches that subjects with low vitamin B12 (cobalamin) had higher concentrations of total homocysteine concentrations (page 68,

lines 1-6). Given the understanding of the metabolism of methionine taught in the specification on pages 1-3, one skilled in the art would recognize that supplying metabolites or cofactors along this pathway, which are downstream of MTRR activity, is useful to treat or prevent diseases associated with MTRR deficiency. Applicants further note that due to the decreased biological activity resulting from an MTRR polymorphism or mutation, the administration of vitamin B12 can be therapeutic, even if the subject has normal levels of vitamin B12. Therefore, one skilled in the art would appreciate that even subjects with normal levels of a metabolite or cofactor will likely benefit from supplemental treatment with one or more of these metabolies or cofactors. As noted above, the specification teaches many formulations and routes of administration to deliver these metabolites and cofactors to patients and experimental animals. In view of these clarifying remarks, this aspect of the rejection may be withdrawn.

Rejection for failure to enable diagnostic methods

The Examiner also states that the invention is not enabling for a method of detecting an increased risk of developing a neural tube defect, Down's syndrome, or cardiovascular disease in any mammalian fetus or embryo that involves detecting any heterozygous or homozygous MTRR polymorphism in a parent, embryo, or fetus. In response to this rejection, Applicants note that the present invention demonstrates that polymorphisms in the human MTRR gene correlate with an increased risk of hyperhomocysteinemia. One aspect of this teaching is that a variety of mutations in the human MTRR gene correlate with disturbances in homocysteine metabolism, such as the A/G polymorphism at nucleotide position 66 and the A/G polymorphism at nucleotide position 110 (see page 56, lines 1-9, of the specification). Such homocysteine metabolic alterations are known to result in hyperhomocysteinemia. Those of ordinary skill in the art would recognize that other polymorphisms in the MTRR gene are likely to

demonstrate a similar correlation and that those mutations that correlate with alteration in homocysteine metabolism are readily identified and distinguished from those mutations which do not alter metabolism. Furthermore, given the conservation of this metabolic pathway, one skilled in the art would appreciate that these mutations are likely to have the same effect in any mammal.

Applicants further note that the invention teaches that mildly elevated homocysteine levels indicate a risk factor for cardiovascular disease, neural tube defects, cancer, and Down's syndrome (page 32, lines 22-24, and page 33, lines 1-4). Furthermore, the specification teaches the identification of subjects at risk for the above-mentioned diseases based on the presence of mutations in the MTRR gene (pages 54-57, page 58, lines 1-2, page 59-61, and page 62-72 of the specification). For example, the Examiner acknowledges that the specification is enabling for demonstrating the correlation between the homozygous A66G MTRR mutation and an increased risk of neural tube defects and demonstrating the correlation between the A66G MTRR mutation and an increased risk for Down's syndrome and coronary artery disease. A skilled artisan would appreciate that this method may be readily applied to detecting any heterozygous or homozygous MTRR polymorphism that is a risk factor for cardiovascular disease, a neural tube defect, Down's syndrome, or cancer. In particular, the specification teaches a repeatable process by which polymorphisms in the MTRR gene are identified and tested for their correlation with increased risk for hyperhomocysteinemia, cardiovascular disease, neural tube defects, Down's syndrome, or cancer (see page 8, lines 14-20; page 13, lines 21-25; and page 14, lines 1-6, of the specification). In order to achieve this, the specification teaches that one needs to: 1) analyze the nucleic acid of a test subject to determine whether the subject contains a mutation in the MTRR gene; and 2) correlate the presence of the mutation to an increased or decreased likelihood of developing hyperhomocysteinemia, cardiovascular disease, neural tube defects, Down's syndrome, or

cancer. With respect to step 1 above, the specification demonstrates how to identify mutations in a MTRR gene (see, for example, page 9, lines 13-22, and page 29, lines 21-22). For example, given the Applicants' disclosure of primers to a mammalian MTRR nucleic acid (see for example, Table 1 and Figure 2), one skilled in the art of molecular biology could readily sequence mammalian MTRR nucleic acids to detect any heterozygous or homozygous polymorphism.

In addition, the specification provides numerous assays that may be used to determine whether a particular MTRR mutation results in decreased or increased MTRR biological activity, and thus is likely correlated with an altered risk for cardiovascular disease, neural tube defects, Down's syndrome, or cancer. For example, a sample from a subject with a particular MTRR mutation may be assayed to measure MTRR enzymatic activity, protein levels, mRNA levels, and/or promoter activity (see page 35, line 24; pages 36-39; and page 40, lines 1-18, of the specification). An MTRR mutation that results in altered MTRR biological activity may be further examined to determine whether the presence of the MTRR mutation is correlated with an increased or decreased likelihood of developing hyperhomocysteinemia, cardiovascular disease, neural tube defects, Down's syndrome, or cancer (step 2). In particular, standard statistical analyses, such as those described on page 48, lines 3-7, of the specification, are used to identify any correlation between MTRR gene polymorphisms and disease (see step 2 above).

Thus, the present invention clearly sets forth a system for identifying any polymorphism in the MTRR gene in any population of individuals (*i.e.,* any mammalian population) and correlating the identified polymorphism as a risk factor for hyperhomocysteinemia, cardiovascular disease, neural tube defects, Down's syndrome, or cancer. It has been established that the specification need not explicitly teach every possible embodiment of the invention. As stated in *Scripps Clinic and Research Foundation v. Genentech, Inc.*, "the purpose of [the enablement] provision is to assure

that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art," See, 18 USPQ2d 1896, 1006 (Fed. Cir. 1991). Similarly, *In re Vaeck*, states that "[t]he first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation'... That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue,'" See, USPQ2d 1438, 1444 (Fed. Cir. 1991).

In summary, the specification provides sufficient guidance and working examples so that no undue experimentation is required to extend the particular findings to any mutation in any mammal. The data would simply be parsed into another polymorphism within a MTRR gene. The key aspect of the present invention is the discovery that polymorphisms in the MTRR gene are associated with hyperhomocysteinemia, cardiovascular disease, neural tube defects, Down's syndrome, and cancer and that this knowledge can be used in the treatment of these diseases. Given this information, any skilled artisan would recognize that this finding can be extended to any MTRR homolog in any mammal. In light of these teachings, Applicants submit that the specification fully enables the claims of the present invention. Therefore, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejections under 35 U.S.C. § 102

Claim 2 and 5 were rejected under 35 U.S.C. § 102, as being anticipated by Mayer et al. (JACC, Vol. 27, No. 3, p. 517-527). The Examiner states that Mayer discloses the administration of folate or cobalamin to patients with coronary atherosclerosis. Claim 2

(from which claim 5 depends) has been amended to delete reference to treatment of cardiovascular disease using folate or cobalamin. In addition, the Applicants have added new claims 27-32 to further clarify the claimed invention. These new claims identify a novel method for the prevention of disease in a test subject. Accordingly, this rejection may be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. A marked-up version indicating the amendments made to the claims, as required by 37 C.F.R. § 1.121(c)(1)(ii), is enclosed. Enclosed is a petition to extend the period for replying for three months, to and including September 5, 2001. Also enclosed is a check in the amount of $141.00 to cover excess claims fees.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 5, 2001

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I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Susan M. Michaud
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Susan M. Michaud
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Gravel et al.	Art Unit:	1633
Serial No.:	09/487,841	Examiner:	Shin-Lin Chen
Filed:	January 19, 2000	Customer No:	21559

Title: (Amended) HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING, AND METHODS FOR EVALUATING RISK OF, PREVENTING, OR TREATING NEURAL TUBE DEFECTS, CARDIOVASCULAR DISEASE, CANCER, AND DOWN'S SYNDROME

Assistant Commissioner for Patents
Washington, D.C. 20231

Version with Markings to Show Changes Made

Marked-up version of the title is presented below.

(Amended) Human Methionine Synthase Reductase: Cloning, and Methods for Evaluating Risk of, Preventing, or Treating Neural Tube Defects, Cardiovascular Disease, Cancer, and Down's Syndrome.

09/25/2002 PZIMMERM 00000002 032095 09487841

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Marked-up versions of claims 1-3 and 5 and new claims 22-34 are presented below.

1. (Amended) A method of [treating or]preventing cancer, cardiovascular disease, Down's syndrome, or neural tube defects in a subject, said method comprising administering to said subject a compound selected from the group consisting of a protein, a small molecule, and an antisense nucleic acid molecule; wherein said compound modulates [inhibiting] methionine synthase reductase biological activity in said subject in an amount sufficient to prevent said cancer, cardiovascular disease, Down's syndrome, or neural tube defect.

2. (Amended) A method of [treating or] preventing [cardiovascular disease or] Down's syndrome, said method comprising administering to the subject [to] a therapeutically effective dose of a metabolite or cofactor selected from the group[:] consisting of folate, cobalamin, S-adenosyl methionine, betaine, and [or] methionine.

3. (Amended) The method of claim 1, [or]2, or 26, wherein said subject has been diagnosed as having a mutation or polymorphism in methionine synthase reductase.

5. (Amended) The method of claim 1, [2, or 4] 26, or 28, wherein said cardiovascular disease is premature coronary artery disease.

22. (New) The method of claim 1, wherein said compound modulates the level of methionine synthase reductase protein or mRNA in said subject.

23. (New) The method of claim 1, wherein said compound modulates the amount of methionine in said subject.

24. (New) The method of claim 1, wherein said compound increases said methionine synthase reductase biological activity.

25. (New) The method of claims 1, wherein said compound decreases said methionine synthase reductase biological activity.

26. (New) A method of treating or preventing cardiovascular disease, said method comprising administering to the subject a therapeutically effective dose of a metabolite or cofactor selected from the group consisting of S-adenosyl methionine, betaine, and methionine.

27. (New) A method of preventing disease in a test subject with an above normal or below normal level of methionine synthase reductase biological activity, said method comprising:

(a) detecting an MTRR mutation or polymorphism that results in altered methionine synthase reductase biological activity; wherein said detection step comprises analyzing a methionine synthase reductase nucleic acid from one or more test subjects selected from the group consisting of a mammal; a potential parent, either male or female; a pregnant mammal; a developing embryo; and a developing fetus; and

(b) administering a therapeutically effective dose of a metabolite or cofactor selected from the group consisting of folate, cobalamin, S-adenosyl methionine, betaine, and methionine to said test subject.

28. (New) The method of claim 27, wherein said disease is a neural tube defect, cardiovascular disease, or Down's syndrome.

29. (New) The method of claim 27, wherein said detection step comprises:

(a) amplifying a methionine synthase reductase nucleic acid in a sample obtained from said test subject; and

(b) sequencing said amplified methionine synthase reductase nucleic acid to detect the presence or absence of a mutation or polymorphism in said methionine synthase reductase nucleic acid.

30. (New) The method of claim 29, wherein said amplification step is performed using one or more primers selected from the group consisting of SEQ ID NO: 3-20.

31. (New) The method of claim 27, comprising administering said metabolite or cofactor to both (i) said pregnant mammal and (ii) said embryo or said fetus.

32. (New) The method of claim 2 or 27, wherein said cobalamin is administered to a subject having a low serum cobalamin level.

33. (New) A method of treating cancer, cardiovascular disease, or a neural tube defect in a subject, said method comprising administering to said subject a compound selected from the group consisting of a protein, a small molecule, and an antisense nucleic acid molecule; wherein said compound modulates methionine synthase reductase biological activity in said subject in an amount sufficient to treat said cancer, cardiovascular disease, or a neural tube defect.

34. (New) The method of claim 33, wherein said subject has cardiovascular disease.